Pediatric Focused Safety Review: Seroquel® (quetiapine fumarate)

Pediatric Advisory Committee Meeting
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Outline

- Background Information
- Pediatric Studies
- Pediatric Labeling Changes
- Additional Relevant Safety Labeling
- Drug Use Trends
- Previous Safety Reviews
- Adverse Events
- Summary

Background Drug Information
Seroquel® (quetiapine fumarate)

- **Drug:** Seroquel® (quetiapine fumarate)
- **Formulation:** oral tablets
- **Therapeutic Category:** antipsychotic (atypical)
- **Sponsor:** AstraZeneca

Background Drug Information (continued)
Seroquel® (quetiapine fumarate)

Indications:

Treatment of schizophrenia: adults and adolescents 13-17 years

Acute treatment of manic episodes associated with bipolar I disorder, as monotherapy and as an adjunct to lithium or divalproex: adults and pediatric patients 10-17 years

Acute treatment of depressive episodes associated with bipolar disorder*: adults

Maintenance treatment of bipolar disorder as an adjunct to lithium or divalproex: adults

**PREA PMR for this indication outstanding*

Background Drug Information (continued)
Seroquel® (quetiapine fumarate)

- **Original Market Approval:**
  September 26, 1997

- **Pediatric Exclusivity Granted:**
  January 23, 2009

- **Pediatric Labeling Changes:**
  December 2, 2009

Pediatric Studies-Efficacy
Seroquel® (quetiapine fumarate)

Treatment of Schizophrenia*

Efficacy was established in a 6-week, double-blind, placebo-controlled, randomized, multicenter parallel-group trial of two target doses of Seroquel® in pediatric patients (13 to 17 years). Seroquel® 400 mg/day (n=73) and 800 mg/day (n=74) demonstrated superiority over placebo (n=75) in the reduction in the total Positive and Negative Syndrome Scale (PANSS) score from baseline.

**Studied under BPCA*

Pediatric Studies-Efficacy (continued) Seroquel® (quetiapine fumarate)

Acute Treatment of Manic Episodes in Bipolar Disorder*

Efficacy was established in a 3-week, double-blind, placebo-controlled, randomized, multicenter, parallel-group trial of two target doses of Seroquel® in pediatric patients (10 to 17 years). Seroquel® 400 mg/day (n=95) and 600 mg/day (n=98) demonstrated superiority over placebo (n=91) in the reduction in the total Young Mania Rating Scale (YMRS) score from baseline.

**Studied under BPCA and PREA*

Pediatric Studies-Safety Seroquel® (quetiapine fumarate)

Safety data were collected during the short-term efficacy studies and a 26-week open-label trial in patients with schizophrenia or bipolar disorder (n=381 enrolled, n=237 completers).

Assessments and variables included:

- Physical examination, vital signs, weight, BMI
- ECG
- Laboratory assessments (hematology, chemistry, lipids, thyroid, prolactin)
- Extrapyramidal symptoms (EPS)
  - Scales: Simpson Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS) and Abnormal Involuntary Movement Scale (AIMS)
  - The incidence of anticholinergic medication use to treat treatment emergent EPS

Pediatric Studies-Safety (continued) Seroquel® (quetiapine fumarate)

No deaths occurred in the clinical trials

A similar percentage of patients had serious adverse events in the quetiapine and placebo groups

The majority of serious adverse events were potentially related to the underlying psychiatric diagnosis

The common adverse events were similar to those identified in the adult clinical trials of quetiapine, i.e. somnolence, dizziness, fatigue, increased appetite, weight increased, nausea, vomiting and dry mouth, **except for a significant increase in pulse, systolic blood pressure and diastolic blood pressure identified in pediatric patients.**

Pediatric Studies-Safety (continued)
Seroquel® (quetiapine fumarate)

Treatment-Emergent Adverse Reactions from the efficacy studies*

	Schizophrenia Study		Bipolar Mania Study	
	Seroquel® (n=147)	Placebo (n=75)	Seroquel® (n=193)	Placebo (n=90)
Somnolence/Sedation	34%	11%	53%	14%
Dizziness	12%	5%	18%	2%
Fatigue	-	-	11%	4%
Increased appetite	-	-	9%	1%
Weight increased	-	-	6%	0%
Nausea	-	-	8%	4%
Vomiting	-	-	8%	3%
Dry Mouth	7%	1%	7%	0%
Tachycardia	7%	0%	7%	0%

**≥5% of Seroquel® treated patients and ≥2x incidence than placebo*

Pediatric Studies-Safety (continued)
Seroquel® (quetiapine fumarate)

Clinically Important Shifts (Select) in Vital Signs+:

	Shift	Quetiapine (n=340)	Placebo (n=165)
Supine pulse (beats per minute)	>120	8.1%	0
	≥15 increase	50.7%	18.4%
Supine Systolic Blood Pressure (mmHg)	>121†	14.2%	5.9%
	≥20 increase	15.2%	5.4%
Supine Diastolic Blood Pressure (mmHg)	≥ 78†	16.8%	7.3%
	≥10 increase	40.6%	24.5%
	≥30 increase	1.5%	1.8%

† *Definitions used for cut-offs differed by gender and age*

Data from the placebo-controlled efficacy studies

Pediatric Labeling Changes
Seroquel® (quetiapine fumarate)

1 Indications:

- 1.1 Schizophrenia (13-17 years)
- 1.2 Bipolar Disorder, Acute Mania (10-17 years)
- 1.3 Special Consideration in Treating Pediatric Schizophrenia and Bipolar Disorder

2 Dosage and Administration:

- 2.1 Schizophrenia 13-17 years*
- 2.2 Bipolar Disorder 10-17 years*

**Information on dose selection and maintenance*

Pediatric Labeling Changes (continued)
Seroquel® (quetiapine fumarate)

5 Warnings and Precautions:

"Children and Adolescents" subheading added to the following five subsections:

- 5.4 Hyperglycemia and Diabetes Mellitus*
- 5.5 Hyperlipidemia*
- 5.6 Weight Gain*
- 5.14 Hypothyroidism
- 5.15 Hyperprolactinemia

- 5.9 Increases in Blood Pressure in Children and Adolescents
- 5.11 Cataracts

**Labeling states that worsening of more than one of the metabolic parameters of weight, blood glucose and lipids was observed in clinical studies. Change in parameters should be managed as clinically appropriate*.

Pediatric Labeling Changes (continued)
Seroquel® (quetiapine fumarate)

5.4 Hyperglycemia and Diabetes Mellitus*

- Labeling provides the mean change in fasting glucose levels for Seroquel® and placebo treated patients in the pediatric schizophrenia and bipolar efficacy trials.
- Labeling states no patient with baseline normal or borderline fasting glucose had treatment-emergent blood glucose ≥126 mg/dL.

5.5 Hyperlipidemia*

- Table with the percentage of patients with changes in total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol from baseline in the efficacy studies provided (See Table 4: Percentage of Children and Adolescents with Shifts in Total Cholesterol, Triglycerides, LDL-Cholesterol and HDL-Cholesterol from Baseline to Clinically Significant Levels: Slide 15).

**This Warning and Precaution has a Children and Adolescents Subheading*

Pediatric Labeling Changes (continued)

Seroquel® (quetiapine fumarate)

5.5 Hyperlipidemia: Table 4: Patients with Changes in Lipids

Laboratory Analyte	Indication	Treatment Arm	N	Patients n (%)
Total Cholesterol ≥200 mg/dL	Schizophrenia[a]	SEROQUEL	107	13 (12%)
		Placebo	56	1 (2%)
	Bipolar Mania[b]	SEROQUEL	159	16 (10%)
		Placebo	66	2 (3%)
Triglycerides ≥150 mg/dL	Schizophrenia[a]	SEROQUEL	103	17 (17%)
		Placebo	51	4 (8%)
	Bipolar Mania[b]	SEROQUEL	149	32 (22%)
		Placebo	60	8 (13%)
LDL-Cholesterol ≥ 130 mg/dL	Schizophrenia[a]	SEROQUEL	112	4 (4%)
		Placebo	60	1 (2%)
	Bipolar Mania[b]	SEROQUEL	169	13 (8%)
		Placebo	74	4 (5%)
HDL-Cholesterol ≤ 40 mg/dL	Schizophrenia[a]	SEROQUEL	104	16 (15%)
		Placebo	54	10 (19%)
	Bipolar Mania[b]	SEROQUEL	154	16 (10%)
		Placebo	61	4 (7%)

Pediatric Labeling Changes (continued)

Seroquel® (quetiapine fumarate)

5.6 Weight Gain*

- Table 5 provides data from efficacy (6 week[a] and 3 week[b]) studies with proportion of patients with weight gain ≥ 7% of body weight:

Table 5 from labeling:

Vital Sign	Indication	Treatment Arm	N	Patients n (%)
Weight Gain ≥7% of Body Weight	Schizophrenia[a]	SEROQUEL	111	23 (21%)
		Placebo	44	3 (7%)
	Bipolar Mania[b]	SEROQUEL	157	18 (12%)
		Placebo	68	0 (0%)

- Mean change in body weight in Seroquel® treated and placebo treated patients in the efficacy studies provided.
- Mean increase in body weight and percentage of patients that gained ≥ 7% of body weight (not adjusted for normal growth) in the long-term/26 week study provided.

**This Warning and Precaution has a Children and Adolescents Subheading*

Pediatric Labeling Changes (continued)
Seroquel® (quetiapine fumarate)

5.9 Increases in Blood Pressure in Children and Adolescents

- The incidence of increases in systolic blood pressure and diastolic blood pressure in Seroquel® treated vs. placebo treated patients in the efficacy studies is provided.
- Data from the long-term study provided: one child with reported history of hypertension experienced a hypertensive crisis.
- "Blood pressure in children and adolescents should be measured at the beginning of, and periodically during treatment".

Pediatric Labeling Changes (continued)
Seroquel® (quetiapine fumarate)

5.14 Hypothyroidism*

The incidence of shifts to potentially clinically important thyroid function values in the efficacy studies for Seroquel® treated and placebo treated patients is provided.

5.15 Hyperprolactinemia*

The incidence of shifts in prolactin levels to clinically significant values in the efficacy studies for Seroquel® treated and placebo treated patients is provided.

**This Warning and Precaution has a Children and Adolescents Subheading*

Pediatric Labeling Changes (continued)

Seroquel® (quetiapine fumarate)

6 Adverse Reactions:

6.1 Clinical Study Experience*

Adverse Reactions in Placebo-Controlled Trials

Data from the schizophrenia and bipolar efficacy trials are provided under separate headings and include:

1. Adverse reactions associated with discontinuation of treatment
2. Commonly observed adverse reactions:
   - The adverse reactions reported in ≥5% of Seroquel® treated patients and ≥2x in placebo treated patients are provided in labeling text and tabular format (See Table 12, slide 20).
   - Potentially dose-related adverse events are provided.

**This Subsection has a Children and Adolescents Subheading*

Pediatric Labeling Changes (continued)

Seroquel® (quetiapine fumarate)

6.1 Clinical Study Experience (continued)

Table 12 from labeling: Treatment-Emergent Adverse Reaction Incidence in 6 Week Placebo-Controlled Clinical Trial for the Treatment of Schizophrenia in Adolescent Patients

Body System/Preferred Term	SEROQUEL (n=147)	PLACEBO (n=75)
Central Nervous System Disorders		
Somnolence[1]	34%	11%
Digestive		
Dry Mouth	7%	1%
Cardiovascular Disorders		
Tachycardia	7%	0%
Nervous system Disorder		
Dizziness	12%	5%

[1]Somnolence combines adverse event terms somnolence and sedation

Pediatric Labeling Changes (continued)
Seroquel® (quetiapine fumarate)

6.1 Clinical Study Experience (continued)

The pooled incidence of commonly observed adverse reactions from the schizophrenia and bipolar efficacy trials are provided.

- Labeling text provides the adverse reactions reported in ≥5% of Seroquel® treated patients and 2x greater than in placebo treated patients, i.e. somnolence (47%), dizziness (15%), fatigue (9%), increased appetite (8%), dry mouth (7%), tachycardia (7%), and weight increased (5%).

- The incidence of adverse reactions in ≥1% of Seroquel® treated patients and greater than placebo are provided in tabular format.

Pediatric Labeling Changes (continued)
Seroquel® (quetiapine fumarate)

6.1 Clinical Study Experience (continued)

Extrapyramidal Symptoms (EPS):

- The aggregated incidence of EPS in both efficacy studies are provided for Seroquel® and placebo treated patients.
- Tables with adverse experiences potentially associated with EPS are provided for both the schizophrenia and bipolar efficacy studies. Tabular data are provided based on Seroquel® dose (See slide 23).

Pediatric Labeling Changes (continued)

Seroquel® (quetiapine fumarate)

6.1 Clinical Study Experience, EPS (continued)

Table 15 from labeling: Adverse experiences potentially associated with EPS from the schizophrenia study:

Preferred Term	Placebo (N=75)		SEROQUEL 400 mg/day (N=73)		SEROQUEL 800 mg/day (N=74)		All SEROQUEL (N=147)	
	n	%	n	%	n	%	n	%
Dystonic event[a]	0	0.0	2	2.7	0	0.0	2	1.4
Parkinsonism[b]	2	2.7	4	5.5	4	5.4	8	5.4
Akathisia[c]	3	4.0	3	4.1	4	5.4	7	4.8
Dyskinetic event[d]	0	0.0	2	2.7	0	0.0	2	1.4
Other Extrapyramidal Event[e]	0	0.0	2	2.7	2	2.7	4	2.7

[a,b,c,d,e] *The terms counted in the "Preferred Term" column are also provided in labeling*

Pediatric Labeling Changes (continued)

Seroquel® (quetiapine fumarate)

6.1 Clinical Study Experience (continued)

Adverse Reactions in Long-Term Open Label Trial

Adverse reactions reported in ≥5% of patients in the 26 week trial are provided in labeling text.

Somnolence	30%
Headache	19%
Increased weight	13%
Vomiting	11%
Nausea	10%
Dizziness	9%
Insomnia	8%

Fatigue	8%
Increased appetite	7%
Upper Respiratory Infection	7%
Agitation	5%
Tachycardia	5%
Irritability	5%

Pediatric Labeling Changes (continued)
Seroquel® (quetiapine fumarate)

6 Adverse Reactions (continued):

6.2 Vital Signs and Laboratory Values*

- Vital sign data are provided for schizophrenia and bipolar efficacy studies.
- The percentage of patients and the number of patients in which potentially clinically significant increases in heart rate occurred are provided for Seroquel® low dose, Seroquel® high dose and placebo.
- Mean increases in heart rate for Seroquel® low dose, Seroquel® high dose and placebo are provided in beats per minute.

**This Subsection has a Children and Adolescents Subheading*

Pediatric Labeling Changes (continued)
Seroquel® (quetiapine fumarate)

8 Special Populations:

8.4 Pediatric Use:

- General comment on adverse reactions in pediatric clinical trials compared to adult clinical trials provided.
- The identified increases in blood pressure are noted.
- Seroquel® indications listed as subheadings, and approved and unapproved pediatric indications identified.
- Brief synopses of the efficacy studies supporting the approved pediatric indications are provided under the indication subheadings.
- Labeling notes some differences in pharmacokinetics (PK) in pediatric patients.

Pediatric Labeling Changes (continued)
Seroquel® (quetiapine fumarate)

12 Clinical Pharmacology*:

12.3 Pharmacokinetics

Similarities and differences between pediatric patients and adults in the quetiapine PK are described.

14 Clinical Studies:

14.1 Schizophrenia*

14.2 Bipolar Disorder/Manic Episodes*

Brief description of the trial design including basis for diagnosis (DSM-IV criteria), randomization scheme, dosing regimen and primary efficacy variable provided for both pediatric efficacy studies.

**This Section or Subsection has a Children and Adolescents Subheading*

Pediatric Labeling Changes (continued)
Seroquel® (quetiapine fumarate)

17 Patient Counseling Information:

Increased Blood Pressure in Children and Adolescents subheading added.

Medication Guide:

Increases in blood pressure reported in children and teenagers included.

List of common possible side effects with Seroquel® in children and adolescents provided.

Additional Relevant Safety Labeling Seroquel® (quetiapine fumarate)

SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SEROQUEL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL is not approved for use in patients under ten years of age [*see Warnings and Precautions* (5.2)].

Additional Relevant Safety Labeling (continued)
Seroquel® (quetiapine fumarate)

5 Warnings and Precautions:

- 5.2 Clinical Worsening and Suicide Risk
- 5.3 Neuroleptic Malignant Syndrome (NMS)
- 5.7 Tardive Dyskinesia
- 5.10 Leukopenia, Neutropenia and Agranulocytosis
- 5.12 QT Prolongation
- 5.13 Seizures
- 5.16 Transaminase Elevations
- 5.17 Potential for Cognitive and Motor Impairment

Additional Relevant Safety Labeling (continued)
Seroquel® (quetiapine fumarate)

5 Warnings and Precautions (continued):

- 5.18 Priapism
- 5.19 Body Temperature Regulation
- 5.21 Suicide
- 5.23 Withdrawal

8 Special Populations:

- 8.1 Pregnancy

  Labeling notes the risk of extrapyramidal and/or withdrawal symptoms in neonates exposed to antipsychotic drugs during the third trimester

10 Overdosage

17 Patient Counseling Information

Medication Guide

Quetiapine Drug Utilization

U.S. Outpatient Retail Pharmacy Setting

December 2009 – July 2011, cumulative[1]

- Total population: 20.5 million prescriptions and 3.3 million patients were dispensed prescriptions for quetiapine products
- Pediatric population: 1.6 million prescriptions and 260,500 patients aged 0 to 17 years received quetiapine products (accounted for 8% of total use)
- Total market share for quetiapine products:
  - 82% Seroquel® products
  - 18% Seroquel XR® products

[1]IMS, Vector One®: National VONA and Total Patient Tracker. December 2009 through July 2011. Data Extracted December 2011.

Quetiapine Drug Utilization (continued)

By Patient Age

U.S. Outpatient Retail Pharmacy Setting
December 2009 – July 2011, cumulative[1]

Quetiapine Products	Patient Count	Share
Total Patients	**3,295,538**	**100.0%**
0-17 years	**260,544**	**7.9%**
18+ years	3,051,073	92.6%
Seroquel®	**2,763,422**	**83.9%**
0-9 years	**32,153**	**1.2%**
10-17 years	**190,094**	**6.9%**
18+ years	2,558,438	92.6%
Seroquel XR®	**822,614**	**25.0%**
0-9 years	**7,044**	**0.9%**
10-17 years	**64,789**	**7.9%**
18+ years	755,451	91.8%

*Unspecified age not included. [1]IMS, Vector One®: Total Patient Tracker. December 2009 through July 2011. Data Extracted December 2011.

Quetiapine Drug Utilization (continued)

Prescribing Specialty and Diagnosis

December 2009 – July 2011, cumulative[1]

- Top prescribing specialties for quetiapine prescriptions: Psychiatry and General Practice/Family Medicine

- Pediatricians accounted for 1% of Seroquel® and less than 1% of Seroquel XR® prescriptions

- Top diagnosis code in pediatric patients:
  - Seroquel®: patients 0-9 years and 10-17 years: "Affective Psychoses" (ICD-9 code 296.9)
  - Seroquel XR®: patients 10-17 years*: "Bipolar Affective" (ICD-9 code 296.7)

  **Diagnoses codes not captured for patients 0-9 years*

[1]IMS, Vector One®: National VONA and SDI, Physician Drug and Diagnosis with Pain Panel. December 2009 through July 2011. Data Extracted September 2011 and December 2011.

Pediatric Safety Reviews

Previous Advisory Committee Discussions Seroquel® (quetiapine fumarate)

Psychopharmacologic Drugs Advisory Committee (June 2009)

- Discussed safety and efficacy issues regarding the approval of quetiapine (and other atypical antipsychotics) in the pediatric population.
- AERS review of adverse event reports associated with quetiapine in patients 0-17 years since product approval (September 1997) with focus on cases of death, metabolic effects, QT prolongation, and Torsades de pointes was performed (May 7, 2009).
  - –Pediatric safety profile determined to be similar to adults
  - –No new safety signals identified

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM164423.pdf

Previous Advisory Committee Discussions (continued)
Seroquel® (quetiapine fumarate)

Pediatric Advisory Committee (December 2009)

- Follow-Up to November 2008 PAC review of olanzapine and risperidone.

- AERS review of adverse event reports focusing on extrapyramidal symptoms, hyperprolactinemia, metabolic effects, and precocious puberty in association with aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone was performed to assess for a differential risk between products or age groups (October 14, 2009).
  - The disproportionality analyses showed increased reporting for metabolic effects in association with olanzapine and quetiapine.

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM191609.pdf

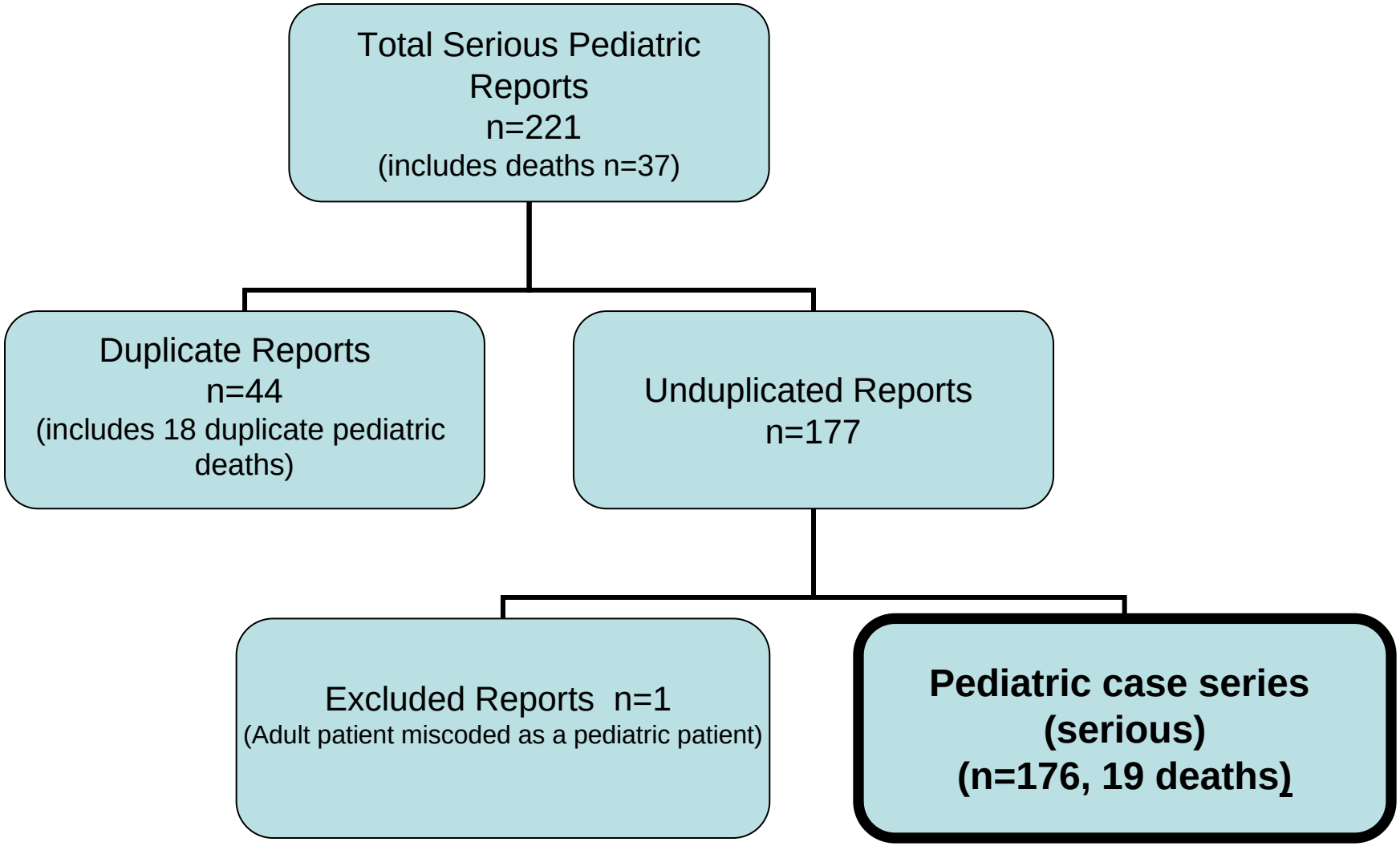
Total Number* of Seroquel® Adverse Event Reports Since Pediatric Approval (December 2, 2009 to July 31, 2011)

	All reports (US)	Serious**(US)	Death (US)
Adults (≥ 17 yrs.)	7463 (5969)	5881 (4463)	986 (751)
Pediatrics (0-16 yrs.)	304 (221)	221 (148)	37 (33)
Unknown Age (Null values)	2848 (2505)	1309 (1013)	149 (118)
All Ages	10615 (8695)	7411 (5624)	1172 (902)

*May include duplicates

**Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

Case Selection



Characteristics of Serious Pediatric Cases Seroquel® (n=176)

- Gender (data from n=172 reports)
  - Male (n=89)
  - Female (n=83)
- Age (data from n=176 reports)
  - 0-< 1 month (n=29)
  - 1 month-< 2 years (n=3)
  - 2-5 years (n=4)
  - 6-12 years (n=32)
  - 12-16 years (n=108)
- Daily Dose (data from n=73 reports)
  - Mean: 588 mg; Median: 250 mg; Range: 12.5 mg to 9600 mg
- Duration of Therapy (data from n=58 reports)
  - Mean: 602 days; Median: 202 days; Range: 1 day to 10 years

Deaths (n=19)
Seroquel® (quetiapine fumarate)

Summary of Pediatric Death Reports:

Self-harm or drug misuse (n=10)

- Suicide: (n=5)
- Toxicity to various agents (n=3)
- Overdose: (n=2)

Cardiac adverse events (n=3)

Miscellaneous (n=6)

Unlabeled adverse events are underlined in all slides

Deaths (continued)
Seroquel® (quetiapine fumarate)

Suicide* (n=5)

- 16 year female died following completed suicide after ingestion of quetiapine, acetaminophen, dextromethorphan, lamotrigine.
- 15 year female died following suspected intentional ingestion of quetiapine and 6 concomitant medications including bupropion, lamotrigine and amphetamine/dextroamphetamine.
- 14 year male died following intentional ingestion of quetiapine resulting in seizure and fatal ventricular fibrillation and cardiac arrest. Concomitant medication: bupropion.
- 15 year female receiving quetiapine and fluoxetine committed suicide by hanging.
- 7 year male being treated with quetiapine, fluoxetine and olanzapine died from suicide after coiling a shower hose around his neck.

** All suicide reports confounded by concomitant medications labeled for suicidality and underlying disorders. Underlying disorders are the strongest predictors of suicide.*

Deaths (continued)
Seroquel® (quetiapine fumarate)

Toxicity to Various Agents (n=3)

- 15 year female died following drug poisoning, prehospital cardiac and respiratory arrest with quetiapine.
- 13 year male with death due to quetiapine toxicity. Patient experienced seizures, coma and death. Report states use of quetiapine was to prevent future seizures. Patient treated with unspecified concomitant medications.
- 10 year male died following prehospital cardiac and/or respiratory arrest due to "acute malicious drug poisoning" with oral omeprazole, quetiapine, risperidone, clonazepam, lorazepam, alprazolam, valproic acid, atomoxetine, methylphenidate, and loratadine.

Deaths (continued)
Seroquel® (quetiapine fumarate)

Overdose (n=2)

- 12 year male died following "stopped breathing" and overdose. Medications included quetiapine, olanzapine, clonazepam, and valproate for unknown indications and durations of therapy.
- 4 year female died from an overdose. Medications included quetiapine, valproate, and clonidine for unknown indications and durations of therapy.

Deaths (continued)
Seroquel® (quetiapine fumarate)

Cardiac adverse events (n=3)

- 13 year female died of cardiomyopathy. Patient was hospitalized while receiving quetiapine 300 mg/day. Cardiomyopathy developed after cessation of quetiapine. Quetiapine was used for an unspecified indication and duration.
- 16 year male died from a heart attack. Duration of therapy, concomitant drug use and relevant medical history not reported.
- "Cardiac arrest" in transplacental exposure at 6 weeks gestation. Abnormal karyotype identified in trophoblasts.

Deaths (continued)
Seroquel® (quetiapine fumarate)

Miscellaneous (n=6)

- Unknown cause (n=2)
  - 4 month infant with toxicology screen positive for quetiapine (170ng/mL) and atropine. Patient not breast fed.
  - 8 year female treated for somnambulism with quetiapine 150 mg at an unknown time and duration prior to death. Patient experienced ketoacidosis, pancreatitis, diabetes (Type I and Type II), and peripheral neuropathy. Concomitant medications included loratadine and methylphenidate.
- One case each: hepatic failure; multi-organ system failure; NMS and QT prolongation; shock due to pancreatitis and diabetic ketoacidosis.

Serious Non-Fatal Adverse Events (n=157) Seroquel® (quetiapine fumarate)

Summary of Serious Non-Fatal Events

- Central Nervous System (n=44)
- Metabolic (n=44)
- Cardiac (n=9)
- Hematologic (n=9)
- Other Serious Miscellaneous Events (n=51)
  - Pregnancy, puerperium and perinatal conditions (n=29)
  - Gastrointestinal (n=7)
  - Injury, poisoning and procedural complications (n=5)
  - General (n=4)
  - Endocrine (n=2)
  - Eye (n=2)
  - Infections and Infestations (n=2)

Serious Non-Fatal Adverse Events (continued)
Seroquel® (quetiapine fumarate)

Central Nervous System (n=44)

- Neuropsychiatric events (n=24)

  –suicidality (n=12); aggression (n=4); self-injurious behavior or ideation (n=3); hallucination (n=2).

  –one case each: abnormal behavior; drug abuse; obsessive compulsive disorder (patient with OCD).

  –17 cases confounded: associated comorbidities, concomitant medications, noncompliance.

- Neuromuscular events (n=14)

  –neuroleptic malignant syndrome (NMS) or NMS-like reaction (n=4); tardive dyskinesia (n=2).

  –one case each: chorea and athetosis; Sydenham's chorea; dystonia; muscle spasm + abdominal pain + pyrexia; muscle twitching + tic + headache; muscle weakness; tremor; withdrawal dyskinesia.

  –5 cases confounded: associated comorbidities, concomitant medications.

Serious Non-Fatal Adverse Events (continued) Seroquel® (quetiapine fumarate)

Central Nervous System (n=44)

- General (n=6)
  - –loss of consciousness (n=3).
  - –one case each: convulsion; sedation; somnolence.
  - –5 cases confounded associated comorbidity, concomitant medications, inappropriate and/or off-label use.

Serious Non-Fatal Adverse Events (continued) Seroquel® (quetiapine fumarate)

Metabolic (n=44)

- Diabetes mellitus (n=29)
  - Type 1 diabetes (n=11), Type 2 diabetes (n=9), unspecified diabetes (n=6), diabetic ketoacidosis (n=2), borderline diabetes/prediabetic (n=1).
  - 25 cases confounded: associated comorbidities, concomitant medications.
- Weight changes (n=12)

  Weight loss (n=1)

  - Concomitant medication: dextroamphetamine/amphetamine labeled for weight loss, anorexia, and decreased appetite.

  Weight gain (n=11):

  - Time to onset 35 days to 3 years, median 202 days (data from n=6).
  - Range of weight gain reported 10 - >100 lbs (data from n=9), See Slide 51.
  - Concomitant medications labeled for weight gain in 8 reports.

Serious Non-Fatal Adverse Events (continued)
Seroquel® (quetiapine fumarate)

Metabolic, Weight gain (cont):

Weight changes reported in the AERS pediatric case series:

Age in Years	Gender	Daily Dose	Amount of Weight Gain or Loss
9	M		
11	F		52 lb weight gain over an unspecified period of time
11	F		13.2 lb weight gain in 7 weeks
12	M		10 lb weight gain per month
12	F	200	43 lb weight *loss* in approximately 1 year
14	M		over 70 lb weight gain over an unspecified period of time
14	F		22 lb weight gain over approximately 1 year
15	F	100	15.4 lb weight gain over 2 months
15	M	800	30 lb weight gain over approximately a 2.5 month period (17 lbs on quetiapine alone, 13 lbs on quetiapine and clozapine)
15	M		over 100 lb weight gain when titrating up to a total of 700mg/day during May 2009
16	F		15 lb weight gain in 1 month after starting quetiapine
16	F		

Blank fields represent information omitted from the AERS report

Serious Non-Fatal Adverse Events (continued)
Seroquel® (quetiapine fumarate)

Metabolic (cont.)

- Hypoglycemia (n=2)
  - 13 year female with 2 years of quetiapine use (dose at report 300 mg/day) for bipolar disorder and mood change, passed out and fell in shower. History of fasting blood glucose "85" and post-prandial blood glucose "62". Hypoglycemia diagnosed at urgent care and sent home. Quetiapine was continued. Concomitant medications: trazodone, clonidine.
  - 16 year male treated with quetiapine 25 mg for depression, hospitalized for hypoglycemia and decreased appetite. Concomitant medication included escitalopram, labeled for decreased appetite.

- Dyslipidemia (n=1)
  - 15 year old male taking quetiapine 50 mg daily for more than 2 years to treat autism, depression, and ADHD, experienced elevated cholesterol (388 mg/dL), triglyceride (1420 mg/dL), glucose (120 mg/dL), AST (47 u/dL), and ALT (68u/dL). "Normalizing" levels reported after discontinuation of quetiapine.

Serious Non-Fatal Adverse Events (continued)
Seroquel® (quetiapine fumarate)

Cardiac Events (n=9)

- QT prolongation (n=3).
- One case each: cardiac arrest ; AV block; cardiac arrest + ventricular fibrillation + QT prolongation; chest pain + EKG abnormal; increased blood pressure; ventricular extrasystole.
- 8 cases confounded by comorbidities and/or concomitant medications labeled for cardiac adverse events

Hematologic Events (n=9)

- leukopenia + neutropenia (n=3); neutropenia (n=2).
- One case each: leukopenia; methemoglobinuria + myoglobinuria + liver function test abnormal; prothrombin time ratio decreased; thrombocytopenia.
- Eight reports confounded by comorbidities or concomitant medications labeled for leukopenia, neutropenia, and/or thrombocytopenia.

Serious Non-Fatal Adverse Events (continued)
Seroquel® (quetiapine fumarate)

Other Serious Miscellaneous Event Reports (n= 51)

Pregnancy, puerperium and perinatal conditions (n=29)

Gastrointestinal (n=7)

- pancreatitis (n=6).
- one case: esophageal spasm (comorbid cerebral palsy, feeding tube, history of gastric ulcer).

Injury, Poisoning and Procedural Complications (n=5)

- accidental drug intake by child (n=2); intentional overdose (n=2).
- one case: fall.

General (n=4)

- drug ineffective (n=2).
- one case each: hypothermia; drug withdrawal syndrome.

Serious Non-Fatal Adverse Events (continued)
Seroquel® (quetiapine fumarate)

Other Serious Adverse Event Reports (continued)

Endocrine (n=2)

- Cushing syndrome
- hypothyroidism

Eye (n=2)

- cataracts

Infection and Infestations (n=2)

- Staphylococcal infection + brain abscess + sinusitis
- pneumonia

Summary Pediatric Focused Safety Review Seroquel® (quetiapine fumarate)

- Based on pediatric clinical trial data, FDA has made extensive changes in quetiapine labeling.
- Labeling provides pediatric data regarding the adverse metabolic effects of quetiapine compared to placebo.
- FDA continues to review additional data from clinical trials regarding pediatric metabolic adverse events related to atypical antipsychotic use.
- FDA recommends continuing routine, ongoing post-marketing safety monitoring.
- Does the Committee concur?

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